## REMARKS

Claims 1-7, 9-11, 13-19, 22, and 25-30 are pending in the application. Claims 1, 2, 10, 13-19, 22, and 25-30 are withdrawn as being drawn to non-elected inventions. Claims 3-7, 9, and 11 are under active consideration. Claim 11 has been amended to further clarify the intended subject matter of the claimed invention. Claim 3 has been amended to address the written description rejection under 35 U.S.C. 112, first paragraph. As amended, claim 3 b) recites a polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1, said polypeptide having phosphatase inhibitory activity, and claim 3 c) recites a biologically active fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:1, said fragment having phosphatase inhibitory activity. Support for the amendment to claim 3 is based on a recent BLAST analysis showing that SEQ ID NO:1 is 99% identical to the calcineurin inhibitor ZAKI-4 (g21307625). See the BLAST analysis attached at Exhibit A and the enclosed article of Cao et al. Biochem. J. 367:459-466 describing the characterization of the phosphatase inhibitory activity of ZAKI-4. Entry of these amendments is respectfully requested. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

**Comments Regarding Restriction Requirement**

Applicants affirm the election with traverse of Group III, which corresponds to claims 3-7, 11, and 12 drawn to polynucleotides.

Applicants reiterate the request that the Examiner withdraw the Restriction Requirement at least with respect to claims 1, 2, 9, 16, and 17 of Group I, and examine those claims together with the elected polynucleotide claims of Group III.

The rules under MPEP section 1893.03(d) require the Examiner to apply the Unity of Invention standard PCT Rule 13.2 instead of U.S. restriction/election of species practice in national stage applications, such as the instant application filed under 35 U.S.C. 371. Applicants believe unity of invention exists for claims drawn to the polypeptide sequence of SEQ ID NO:1 (*i.e.*, claims 1, 2, 9, 16, and 17) and claims drawn to the elected polynucleotide sequence of SEQ ID NO:31 which encodes SEQ ID NO:3 (*i.e.*, claims 3-7, 11, and 12) based on the rules

concerning unity of invention under the Patent Cooperation Treaty. The Administrative Instructions Under The Patent Cooperation Treaty, Annex B, Unity of Invention, Part 2, "Examples Concerning Unity of Invention" provide the following guidelines with regard to unity of invention between a protein and the polynucleotide that encodes it:

> *Example 17*
> Claim 1: Protein X.
> Claim 2: DNA sequence encoding protein X.
> Expression of the DNA sequence in a host results in the production of a protein which is determined by the DNA sequence. The protein and the DNA sequence exhibit corresponding special technical features. Unity between claims 1 and 2 is accepted.

Applicants submit that Example 17 does apply to the claims of the instant application, since the polynucleotide of SEQ ID NO:3 does encode the polypeptide of SEQ ID NO:1. In particular, claims 1 and 3 meet the unity of invention standard. Claim 3 recites an isolated polynucleotide encoding a polypeptide of claim 1. Unity of invention is accepted between a protein and the polynucleotide that encodes it. The refusal to examine claims drawn to polynucleotides and polypeptides together on the grounds that the polynucleotide is structurally distinct from the polypeptide is improper.

**Rejoinder of method claims upon allowance of product claims under U.S. practice**

The Examiner is reminded that 9 (Group I), 13 (Group XIII) and 28 (Group XXI), drawn to methods of using the elected polynucleotides of Group III should be rejoined per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants request that claims 9, 13, and 28 be rejoined and examined upon allowance of the claims drawn to the polynucleotides of Group III.

**Objection to the Specification**

The Examiner also objected to the presence of references to hyperlinks and/or other forms of browser-executable code in the specification (Office Action, page 7). Applicants did not intend to have active links in the specification, nor to incorporate the subject matter of web sites by reference to such hyperlinks. Applicants have amended the specification to remove active

hyperlinks and therefore respectfully request that the Examiner withdraw the objection to the specification.

**Written description rejections under 35 U.S.C. § 112, first paragraph**

Claims 3-7, 9, and 11 have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (footnotes omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:3 are specifically disclosed in the application (see, for example, page 2, lines 26-34). Variants of SEQ ID NO:3 are described, for example, at page 3, lines 28-34 and page 22, lines 10-18. Incyte clones in which the nucleic acids encoding the human detoxification protein DETX-1 were first identified and libraries from which those clones were isolated are described, for example, at Table 4. Chemical and structural features of SEQ ID

NO:1 are described, for example, at Table 2. Given SEQ ID NO:1, one of ordinary skill in the art would recognize an isolated polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1. Given SEQ ID NO:3, one of ordinary skill in the art would recognize a polynucleotide comprising a naturally occurring polynucleotide sequence having at least 70% sequence identity to the polynucleotide sequence of SEQ ID NO:3. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

The Specification at page 8, lines 4-6, defines "DETX" as "the amino acid sequences of substantially purified DETX obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant." Hence, by referring to polynucleotides encoding DETX, the Applicants clearly contemplated polynucleotides encoding SEQ ID NO:1 as well as naturally occurring variants thereof.

Additionally, the term "naturally occurring" is a well-known term in the art which Applicants intended to be used in such context. As such, no further definition of the term is necessary (MPEP 2163 IIA3(a)):

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

One of ordinary skill in the art would recognize that "a naturally occurring polynucleotide sequence" as recited in claim 11 is one which occurs in nature. Through the process of natural selection, nature will have determined the appropriate polynucleotide sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of DETX-1) and SEQ ID NO:3 (the polynucleotide sequence encoding DETX-1), one of skill in the art would be able to routinely obtain a polynucleotide encoding "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" or a polynucleotide sequence having at least 70% sequence identity to the polynucleotide sequence of SEQ ID NO:3. For example,

the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application (See Specification, *e.g.*, at p 29, lines 24-34; p. 45, lines 14-31; and Example VII at p. 57).

Applicants respectfully point out that the claims are directed to polynucleotides, not polypeptides, and it is the functionality of the claimed polynucleotides, not the polypeptides encoded by them, that is relevant. Members of the claimed genus of variants may include, for example, mutant alleles associated with diseases, or single nucleotide polymorphisms (SNPs). Members of the claimed genus of variants may encode defective polypeptides, including variants that may be associated with disease states, such as the diseases listed on page 45, line 34 through page 46, line 19, of the specification.

The Office Action has further asserted that the claims are not supported by an adequate written description because "[t]he specification discloses only 2 species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus" (Office Action at page 8).

Such a position is believed to present a misapplication of the law.

**1. The present claims specifically define the claimed genus through the recitation of chemical structure**

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional

characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than functional characteristics. For example, the "variant language" of independent claims 3 and 11 recite chemical structure to define the claimed genus:

3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:...

b) a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1, said polypeptide having phosphatase inhibitory activity...

11. An isolated polynucleotide selected from the group consisting of:...

b) a polynucleotide comprising a naturally occurring polynucleotide sequence having at least 90% sequence identity to the polynucleotide sequence of SEQ ID NO:3...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

**2. The present claims do not define a genus which is "highly variant"**

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et

al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to human detoxification proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as human detoxification proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 234 amino acid residues). This variation is far less than that of all potential human detoxification proteins related to SEQ ID NO:1, i.e., those human detoxification proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

### 3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of July 7, 1999. Much has happened in the development of recombinant DNA technology in the 20 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:3, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

**4. Summary**

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 or SEQ ID NO:3. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

**Double Patenting Rejection**

Claims 3-7, 9, and 11 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,524,819. Applicants request that the requirement for submission of a Terminal Disclaimer with respect to U.S. Patent No. 6,524,819 be held in abeyance until there is an indication of allowable subject matter in the present application.

## CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. 09-0108.

Respectfully submitted,
INCYTE CORPORATION

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Enclosures:

1. Brenner et al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998).
2. Cao et al. Biochem. J. 367:459-466 (2002).
3. Exhibit A